Abstract

Development of PET Methods for Imaging Addiction:
Imaging the mGluR5 and detecting smoking-induced dopamine release

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Brain imaging with positron emission tomography (PET) has advanced the study of addiction and the development of pharmacotherapies to treat addiction. In the study of nicotine addiction and smoking, attempts to measure smoking-induced dopamine (DA) release with PET have met with varying levels of success.

Nicotine has been shown to induce DA release in animal studies. However, the effect is mild and violates the assumption of non-varying endogenous neurotransmitter, which is required kinetic models to estimate tracer binding potential (BP_{ND}). We conducted simulation studies to evaluate the ability of conventional models to detect smoking-induced DA release as decrease in BP_{ND}. We also developed advanced experimental and analysis methods to increase the detectability of smoking-induced DA release by PET. We conducted scans during which subjects smoked in a block design while within the scanner to increase the value of the data and decrease analysis ambiguity. To analyze smoking scan data without violating assumptions of conventional models, we adapted the linear extension of the simplified reference region model (LSRRM) to fit the data. LSRRM is an advanced model which allows for time-variation in endogenous neurotransmitter.

Much of PET imaging of addiction to date has focused the mesolimbic DA system, but less is known about the effects of addiction on other neurotransmitter systems. Glutamate has been implicated in various forms of addiction, and antagonists for the metabotropic glutamate subtype 5 receptor (mGluR5) have recently been suggested as possible treatment options for addiction. [^{18}F]FPEB is a PET tracer which, in preclinical studies, has shown high specificity and selectivity toward the mGluR5. To define optimal scan methodology, we scanned healthy human subjects for 6 h following either a bolus injection (n=5) or bolus-plus-constant-infusion (n=5) of [18F]FPEB. We tested [^{18}F]FPEB data with a variety of PET modeling methods and found it to be an excellent tracer with low which could be analyzed successfully by different methods. The development of this new tracer, including determining the optimum scanning protocol, analysis methods, and reliability in human studies, will allow for future study of the effects of drug abuse and addiction on the glutamate system.